IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Guillermo J. Tearney et al.		
Application No.:	10/016,244		
Filing Date:	October 30, 2001	Examiner:	Shawna Jeannine Shaw
Title:	OPTICAL METHODS AND SYSTEMS FOR TISSUE ANALYSIS	Group Art Unit:	3737

DECLARATION UNDER 37 C.F.R. § 1.131

We, GUILLERMO J. TEARNEY and BRETT E. BOUMA, hereby declare as follows:

1. We are the joint inventors of the invention disclosed and claimed in U.S. Patent Application Serial No. 10/016,244 filed October 30, 2001 (the "'244 App."), which claims priority under 35 U.S.C. § 119(e) from U.S. Patent Application Serial No. 60/244,255 filed October 30, 2000 (the "'255 App.").

2. At the time the invention was made, we were employed by The General Hospital Corporation, the assignee of the entire right and interest to the above-identified application. We continue to be employed by The General Hospital Corporation.

3. We conceived the subject matter of the invention recited at least in independent claims 1 and 39 in the '244 App. (as amended in the attached Amendment) and described in the '255 App. on or before May 3, 2000. Further, the invention recited in pending claims 1 and 39 was reduced to practice at least as early as the filing date of the '255 application. We diligently worked on reducing the claimed invention to practice from the date of the conception thereof by providing the disclosure to a patent attorney, and working diligently with such patent attorney to file the '255 App.

4. In particular, on or before May 3, 2000, we conceived a method of analyzing tissue, in which a tissue is illuminated with coherent or partially coherent light, light reflected from the tissue is received at a detector, and a series of speckle patterns are formed, and changes in the speckle patterns are analyzed at time intervals sufficient to measure changes caused by microscopic motion of objects within the tissue, such that

the tissue is in vivo and/or the tissue is internal tissue (as recited in amended independent claims 1 and 39). This method was reduced to practice upon the filing of the '255 App.

5. In addition, on or before May 3, 2000, we conceived to practice a method of analyzing a tissue structure, in which a tissue is illuminated with coherent or partially coherent light, light reflected from the tissue is received at a detector, and a series of speckle patterns are formed such that the tissue is in vivo and/or the tissue is internal tissue, and speckle pattern data at time intervals sufficient to measure microscopic motion within the tissue structure or adjacent tissue, and the tissue structure is assessed by analyzing spatial characteristics of the speckle pattern data to deduce structural or biomechanical characteristics of the tissue structure (as recited in amended independent claim 39). This method was also reduced to practice upon the filing of the '255 App.

6. As evidence of the conception of the invention recited in amended independent claims 1 and 39 on or before May 3, 2000, attached hereto as Exhibit A is a copy of the eighteen (18) page presentation document entitled "Vulnerable Plaque Characterization Using Temporal and Spatial Speckle Analysis" (referred to herein below as "Presentation") which was prepared internally at least as early as May 3, 2000.

7. The attached document demonstrates that we conceived the method of the invention to analyze tissue and tissue structure at least as early as the completion date of the Presentation (i.e., on or before May 3, 2000). For example, the Presentation describes a receipt of a coherent interference of light remitted from a scattering media or substrate. (see, e.g., Presentation, p. 7). Further, the Presentation describes the formation of speckle patterns to be detected by indicating that, e.g.,

> "Motion of a single scatterer in the specimen changes the speckle pattern
> • The time dependent speckle pattern can be used to determine the Brownian motion within a multiply scattering media
> • The motion is characterized by the spatial decorrelation of the speckle pattern as a function of time
> • For Brownian motion, the decorrelation is a negative exponential with a time constant, τ" (see *id.*)

8. In addition, the Presentation describes a determination of microscopic motion within the tissue and/or adjacent to the tissue, and also determining the spatial characteristics of speckle pattern data. For example, it is provided as follows:

"Spatial and Temporal Characterization of Plaques

Measuring the speckle decorrelation time, τ, as a function of distance from beam entry point allows measurement of Brownian Motion and
- Cap thickness
- Cap stiffness
- Lipid pool stiffness" (see *id.*, p. 9).

9. The tissues being discussed in the Presentation are clearly provided in vivo and/or are internal tissues by referring to IVUS and OCT techniques which measure the tissues in vivo and/or internal tissues. Further, the Presentation describes the determination of the structural or biomechanical characteristics of the tissue structure. (See *id.*, pp. 3-5).

10. The invention as recited in now-pending independent claims 1 and 39 has been reduced to practice by filing the '255 App., which completely describes each of the features recited in these claims. For example, the '255 App. (a copy of which is attached herewith as Exhibit B), at least on pages 1-4 as well as in other portions thereof, clearly describes each and every feature recited in these claims.

11. We further declare that all statements made herein of our own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements are made with the knowledge that the making of willfully false statements and the like is punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and may jeopardize the validity of any patent issuing thereon.

6/3/05
Date

GUILLERMO J. TEARNEY

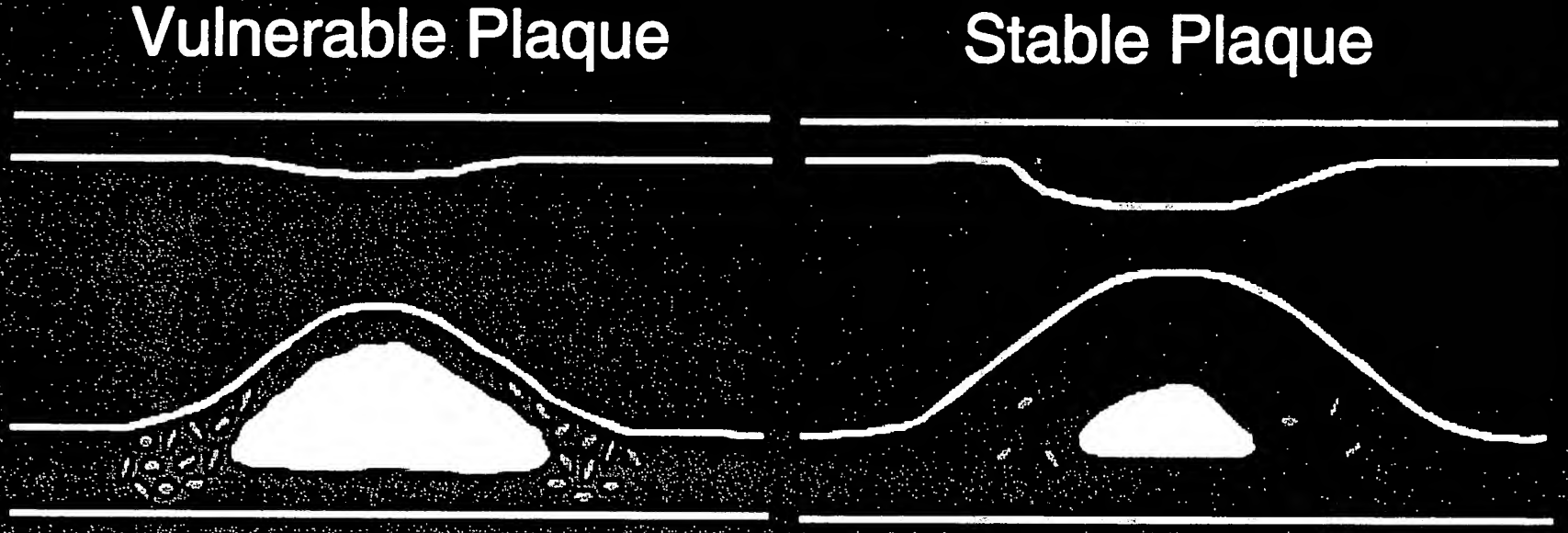
6/3/05
Date

BRETT E. BOUMA

Vulnerable Plaque Characterization Using Temporal and Spatial Speckle Analysis

Gary J. Tearney, M.D. Ph.D.
Massachusetts General Hospital
Department of Pathology and
Wellman Laboratories of Photomedicine

Vulnerable Plaques



Thin —— Cap —— Thick

Abundant —— Macrophages —— Few

High —— Lipid Conc. —— Low

Vulnerable Plaque Diagnosis

Proposed Diagnostics

- Infrared
  - Indirectly measures lipid content of plaque
- Fluorescence
  - Measures autofluorescence
    - Collagen
    - MMP
- IVUS
  - Structural measurement of cap
  - Poor resolution
- OCT
  - Structural measurement of cap
  - Sufficient resolution for measurement of cap thickness

Proposed methods do not measure the biomechanical properties of plaque

Intrinsic Plaque Biomechanics

Biomechanical properties

- Cap strength
  - **Proportional to thickness and structural integrity**
- Lipid pool
  - **Shear stress and strain on cap are related to lipid pool stiffness**
  - **Rupture of plaque tends to occur in areas of large stiffness gradient between cap and lipid pool**
  - **Lipid lowering drugs increase stiffness of lipid pool**
  - **Stiffening of the lipid pool decreases vulnerability**

Mechanical stiffness of the cap and lipid pool are essential parameters for assessing the likelihood of plaque rupture

Viscosity

Viscosity of tissue is proportional to stiffness

- Related to the ability of the molecules in the tissue matrix to move

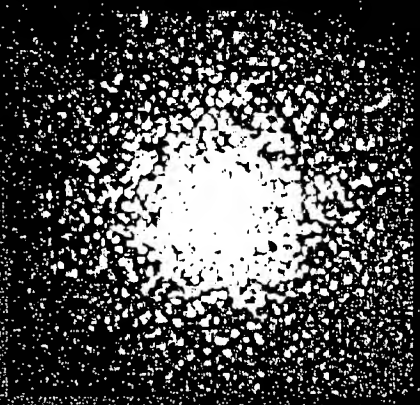
Brownian motion

- Random motion of particles in the matrix
- Brownian motion is inversely proportional to viscosity and stiffness
  - **Low stiffness, rapid Brownian motion**
  - **High stiffness, slow Brownian motion**

Brownian motion velocity is a measurement of tissue stiffness

Speckle

Coherent interference of light remitted from a scattering media or substrate



- Produces a grainy pattern at the surface of the specimen and in the image plane
- The pattern is created from the remitted field after many multiple scattering events within the specimen
- Motion of a single scatterer in the specimen changes the speckle pattern

Speckle Motion

Motion of a single scatterer in the specimen changes the speckle pattern

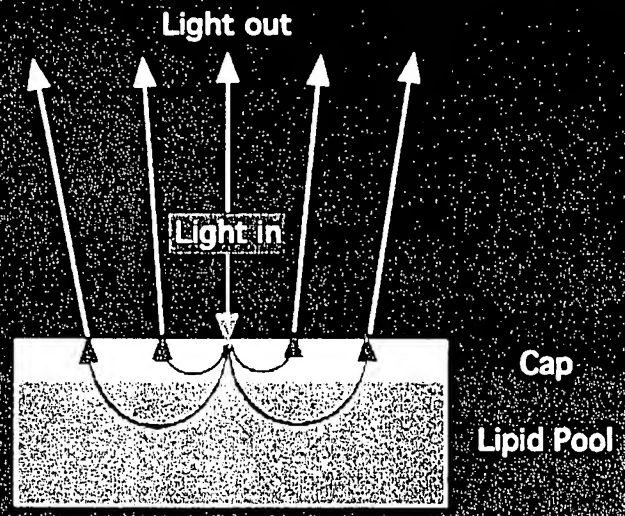
- The time dependent speckle pattern can be used to determine the Brownian motion within a multiply scattering media
- The motion is characterized by the spatial decorrelation of the speckle pattern as a function of time
- For Brownian motion, the decorrelation is a negative exponential with a time constant, τ

Stiffness of the cap and lipid pool can be determined by measuring the speckle decorrelation time constant

Light Diffusion

In tissue, light remitted further from the beam entry point has probed deeper into the tissue

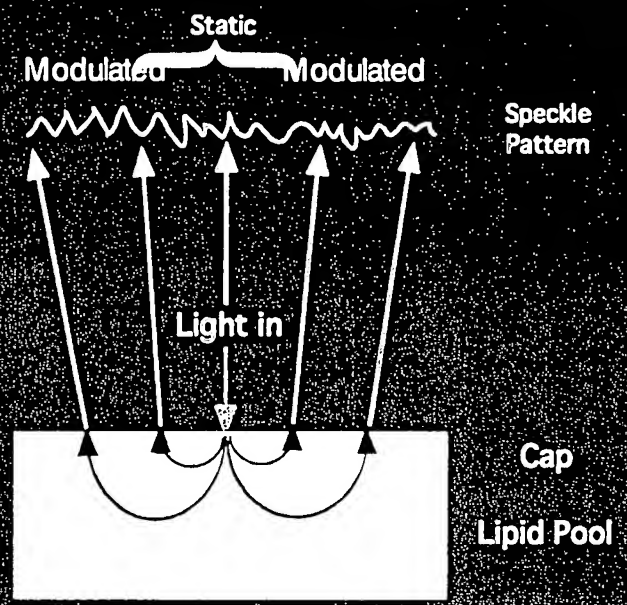
- Governed by the optical properties of tissue



Spatial and Temporal Characterization of Plaques

Measuring the speckle decorrelation time, τ, as a function of distance from beam entry point allows measurement of Brownian Motion and

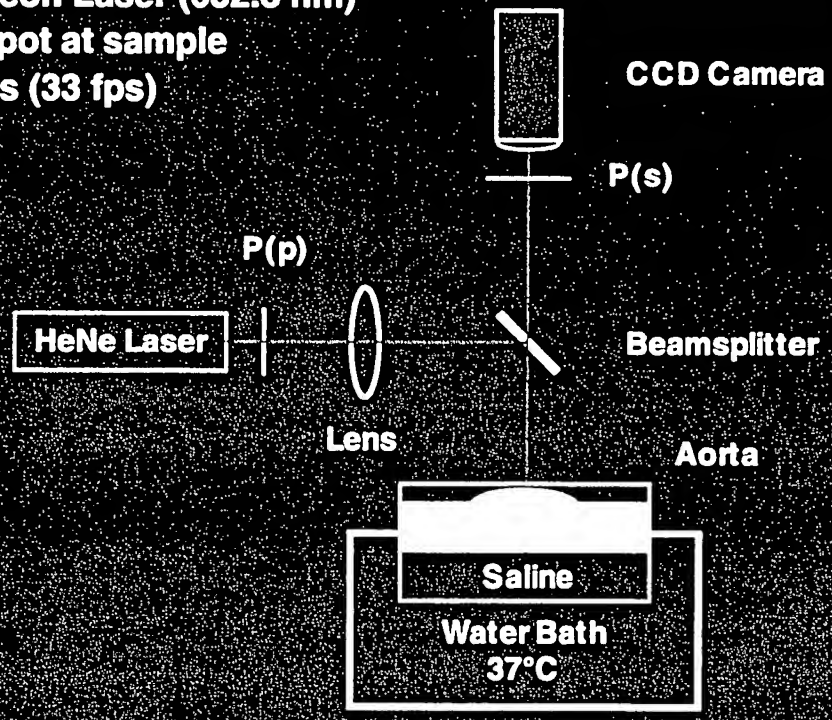
- Cap thickness
- Cap stiffness
- Lipid pool stiffness



Proof of Principle

Methods

- Cadaveric aortas
- Normal saline, 37°C
- Helium Neon Laser (632.8 nm)
- 100 μm spot at sample
- 2 seconds (33 fps)



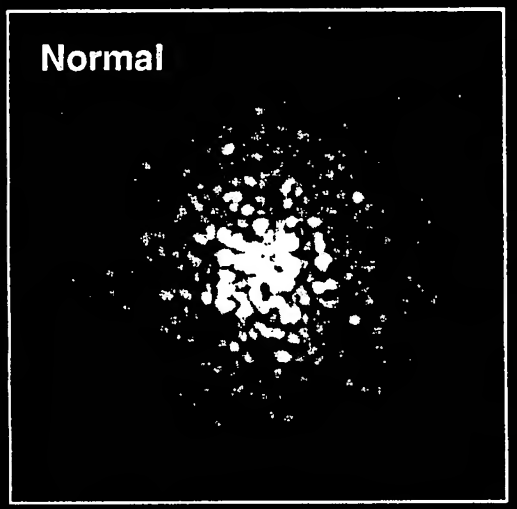
Results

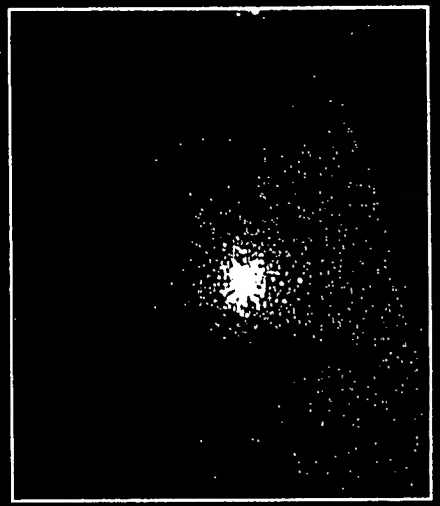
Speckle

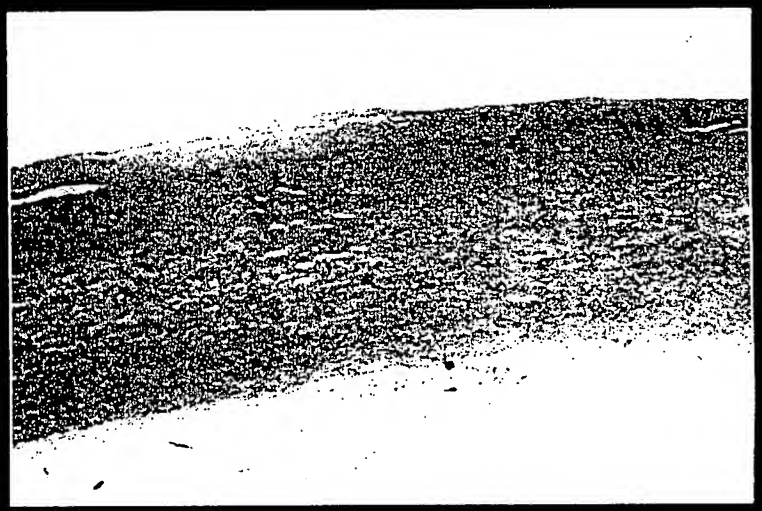
Visible

Histology

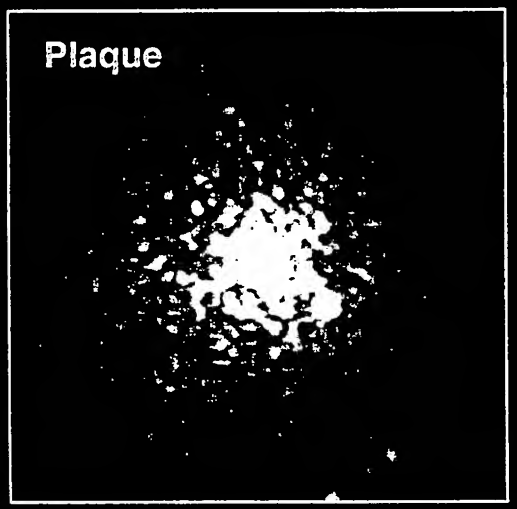
Normal

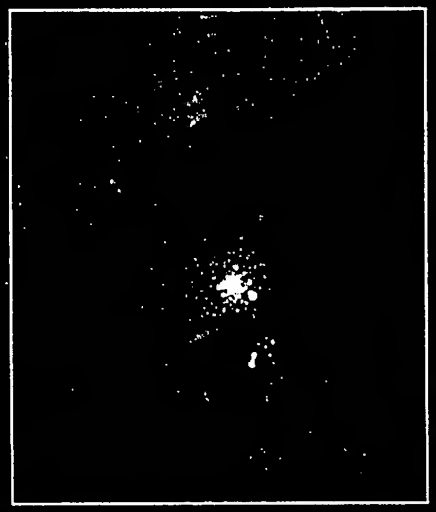


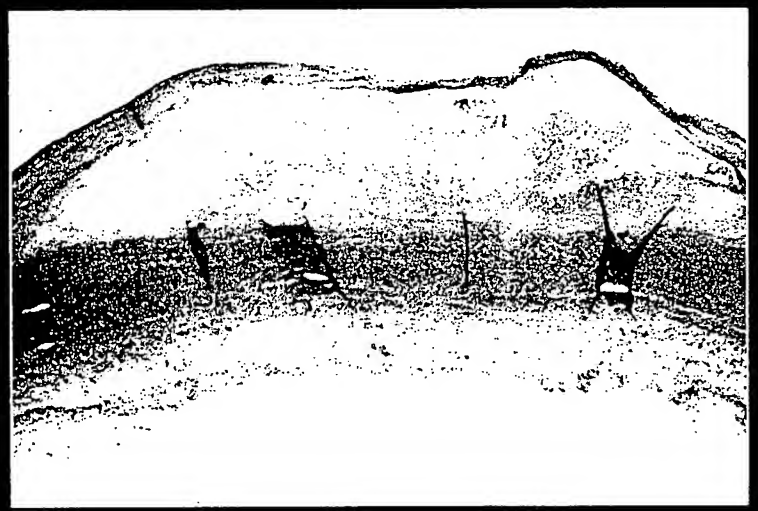


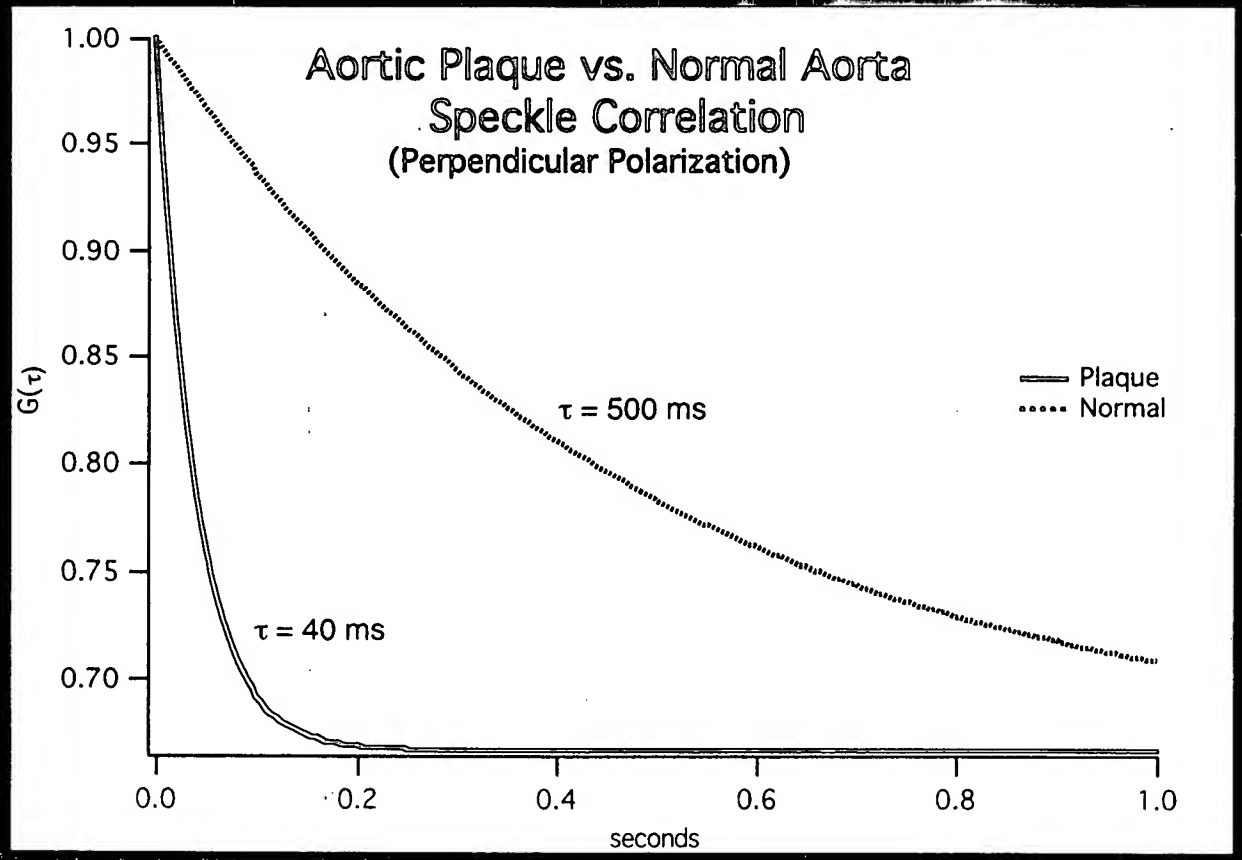


Plaque







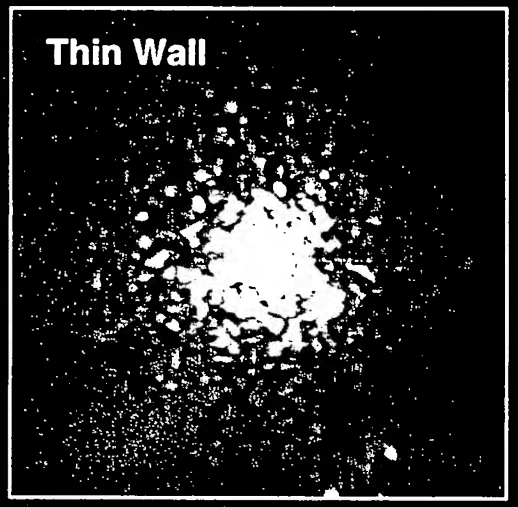

Aortic Plaque vs. Normal Aorta
Speckle Correlation
(Perpendicular Polarization)
1.00
0.95
0.90
0.85
0.80
0.75
0.70
G(τ)
τ = 500 ms
τ = 40 ms
Plaque
Normal
0.0
0.2
0.4
0.6
0.8
1.0
seconds

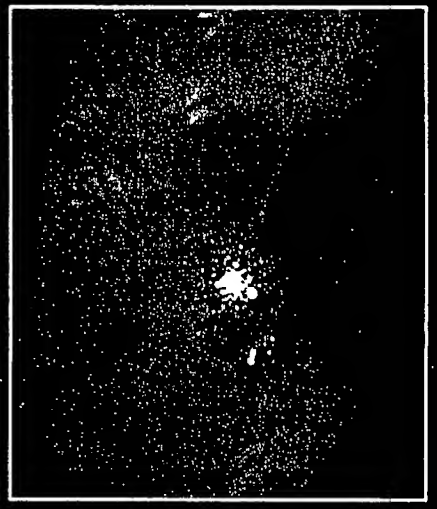
Speckle

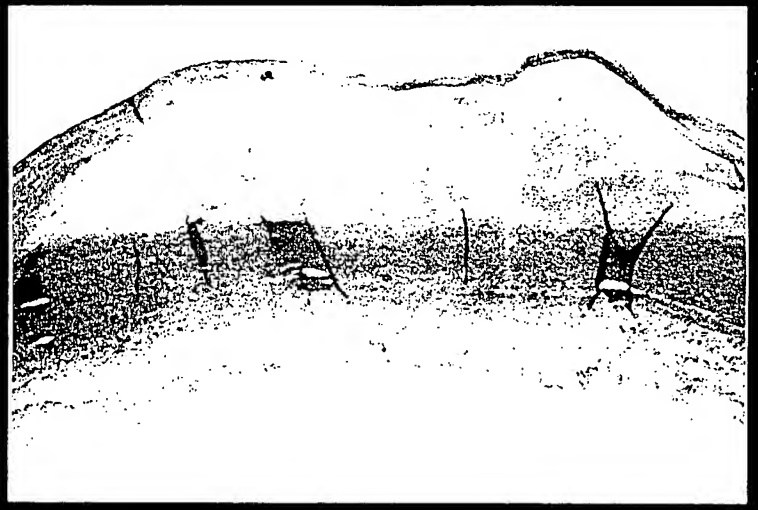
Visible

Histology

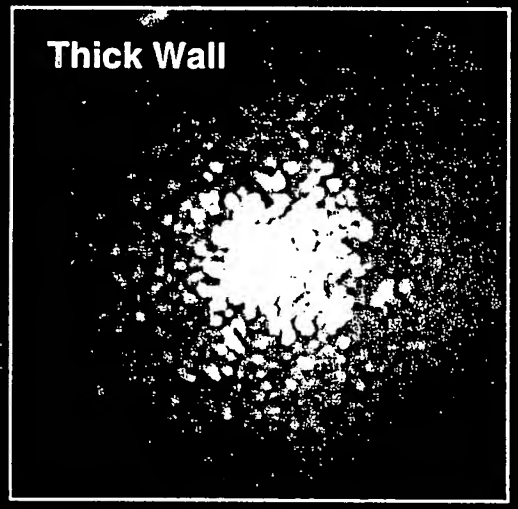
Thin Wall

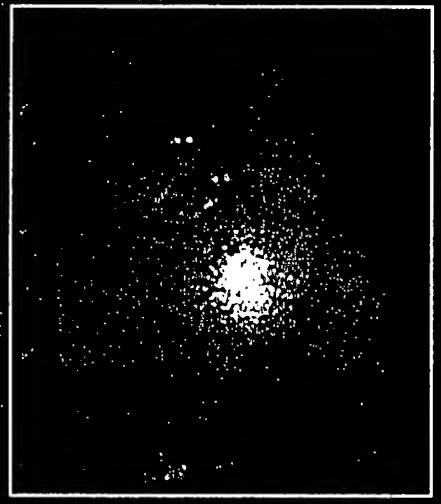


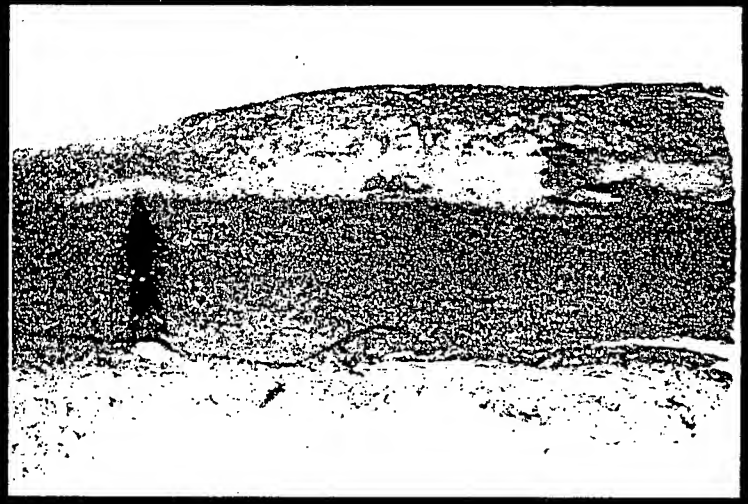


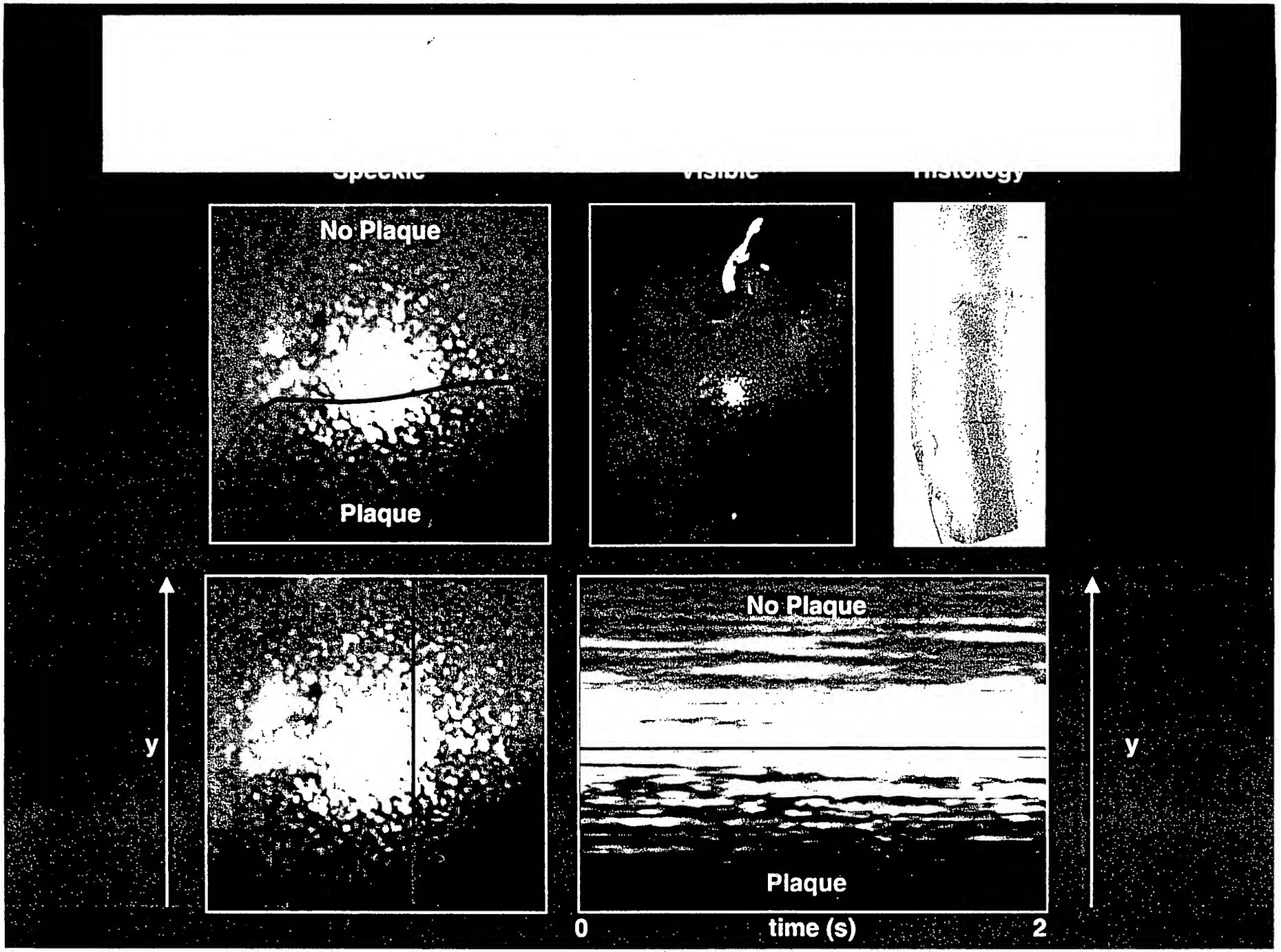


Thick Wall








No Plaque
Plaque
y
No Plaque
Plaque
0
time (s)
2
y

Feasibility Study Summary

Speckle decorrelation time constant is different between normal aorta and plaque

- τ = 500 ms vs 40 ms

Speckle decorrelation time constant is different between thin and thick-walled plaques

- Greater for thick-walled plaques

Speckle decorrelation is spatially dependent

- Border between plaque and normal aorta demarcates different speckle decorrelation time constants

Clinical Realization

Catheter based technique (one possibility)

- Array of fibers
- Scanned probe

Difficulties

- Intrinsic heart and catheter motion
  - **Lipid pool Brownian motion time constant is approximately 40 ms**
- Blood
  - **Will need saline infusion and/or direct contact with tissue**

Localize time and space (x, y, z) dependent speckle patterns using optical methods as opposed to light diffusion

- Confocal microscopy
  - Apertures in the source and detector planes combined with a high numerical aperture imaging lens
  - High resolution speckle analysis in (x, y, z)
  - Speckle decorrelation is less sensitive than multiple scattering technique
- Optical Coherence Tomography (OCT)
  - Uses low coherence interferometry to obtain localization in z
  - Measures cap thickness directly
  - Speckle decorrelation is less sensitive than multiple scattering technique

Conclusion

Temporal and spatial analysis of the speckle patterns can potentially determine

- Cap thickness
- Cap and plaque viscosity
- Spatially resolved biomechanical stiffness
- Plaque vulnerability

Future work

- Speckle statistics
  - **Can determine cap thickness and optical properties**
  - **Low coherence light**
- Strain and stress measurements
  - **Correlate biomechanical properties with Brownian motion measured by speckle decorrelation**
- Probe development
- Continue cadaveric aorta studies
- In vivo studies (e.g. rabbit model)

 JPF DYS

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/244,255	10/30/2000		75	00786-443P01/MGH - 1542	7		

FILING RECEIPT

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Applicant(s)

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Brett E. Bouma, Quincy, MA ;

Continuing Data as Claimed by Applicant

Foreign Applications

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Title

Optical methods and systems for tissue analysis

Preliminary Class

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Attorney's Docket No.: 00786-443P01 / MGH - 1542

PROVISIONAL APPLICATION FOR PATENT

under

37 CFR §1.53(c)

TITLE: OPTICAL METHODS AND SYSTEMS FOR TISSUE ANALYSIS

APPLICANT: GUILLERMO J. TEARNEY AND BRETT E. BOUMA

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October 30, 2000
Date of Deposit

Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

Optical Methods and Systems for Tissue Analysis

TECHNICAL FIELD

The invention relates to tissue analysis, and more particularly to characterizing tissue by analyzing speckle patterns formed by light reflected from tissue.

BACKGROUND

"Speckle" is an interference phenomenon that occurs when coherent light (e.g., laser light) is reflected from a rough or multiply scattering sample onto a detection plane. Due to scattering of photons from and within the sample, different photons travel different distances to the detection plane. As a result, the light reflected or backscattered from the sample, if spatially and temporally coherent, interferes at the detection plane, producing a grainy pattern known as "speckle."

Researchers have used speckle pattern analysis to study dynamic movement of tissue *in vivo*. For example, speckle has been used to measure vibrations of tissue, V. Tuchin et al., "Speckle interferometry in the measurements of biotissues vibrations," SPIE, 1647: 125 (1992), and to measure strain in vascular and cortical tissue in response to forced movement of the tissue, Sean J. Kirpatrick et al., "Laser Speckle Microstrain Measurement in Vascular Tissue," SPIE, 3598: 121-128 (1999); and Sean J. Kirkpatrick and Brent W. Brooks, "Micromechanical Behavior of Cortical Bone as Inferred from Laser Speckle Data," J. Biomedical Materials Research, 39(3): 373-79 (1998). Researchers have also used speckle to study blood flow and lymph flow. B. Ruth, "Blood Flow Determination by the Laser Speckle Method," Int'l J. Microcirc: Clinical and Experimental, 9(1): 21-45 (1990); and A.A. Bednov et al., "Investigation of Statistical Properties of Lymph Flow Dynamics Using Speckle-Microscopy," SPIE, 2981: 181-90 (1997).

SUMMARY

The invention is based on the discovery that tissues can be analyzed *in vivo* using laser speckle to measure Brownian motion.

In general, the invention features a method of analyzing tissue, e.g., *in vivo*, by illuminating a tissue with coherent light, such as laser light; receiving light reflected from the tissue at a detector to form a series of speckle patterns; and analyzing changes in the speckle

patterns at time intervals sufficient to measure changes caused by Brownian motion of objects within the tissue. For example, the speckle pattern can be a far field image formed at the detector. The method can further include compensating for extrinsic motion, such as a heartbeat, to isolate the Brownian motion. In this method, the illuminating step can include providing an invasive device coupled to a light source, passing the device into a patient, placing the device in proximity to the tissue, and shining coherent light from the light source onto the tissue.

The invasive device can be, e.g., a catheter, an endoscope, or a laparoscope. The device can be placed in direct contact with the tissue. The device can include a catheter having a first fiber that transmits light from the light source to the tissue, and a fiber array that receives light remitted from the tissue. The analyzing step can include comparing each of the series of speckle patterns to a reference speckle pattern, and quantifying the differences between each pattern and the reference pattern. For example, the analyzing step can include digitizing each of the speckle patterns, and the quantifying step can include evaluating a maximum cross-correlation between each pattern and the reference pattern. The analyzing step can further include determining a decorrelation rate for the speckle patterns, or analyzing spatial characteristics of the speckle pattern to deduce structural characteristics of the tissue.

In variations, the method can include illuminating multiple sections of the tissue in succession, forming a separate series of speckle patterns for each respective section of the tissue, and then analyzing each separate series of speckle patterns and comparing the separate series to deduce structural differences between the respective sections of the tissue.

In certain embodiments, the method includes gathering reflected light at a light receptor and transmitting the gathered light to the detector, and compensating for extrinsic motion by coupling the receptor to the tissue. Compensating for extrinsic motion can also be done by excluding changes in the speckle patterns caused by non-random motion during the analysis step. Extrinsic motion can also result, for example, from blood flowing between the tissue and the reflector. In those cases, the compensating step can include replacing the blood with a transparent solution.

In another embodiment, the invention features a method of determining the susceptibility to rupture of an atherosclerotic plaque having a lipid pool and a fibrous cap. The method includes illuminating the plaque with coherent light; receiving light reflected

from the plaque at a detector to form a series of speckle patterns; gathering speckle pattern data at time intervals sufficient to measure Brownian motion within the lipid pool; and assessing the plaque's vulnerability to rupture from the amount of Brownian motion.

The method can further include analyzing spatial characteristics of the speckle pattern data to determine structural characteristics of the plaque, for example, by assessing the thickness of the fibrous cap. In that case, a plaque is considered vulnerable to rupture if the thickness of the fibrous cap is less than about 60 microns. The method can also be used to assess the viscosity of the lipid pool, wherein the plaque is considered vulnerable to rupture if the viscosity of the lipid pool has a time constant of less than about 200 milliseconds, and considered likely to rupture if the viscosity of the lipid pool has a time constant of less than about 100 milliseconds.

The invention also includes a method of detecting a vulnerable atherosclerotic plaque having a lipid pool and a fibrous cap within a blood vessel by illuminating a segment of the blood vessel in vivo with coherent light; receiving light reflected from the interior vessel wall of the segment at a detector to form a series of speckle patterns; gathering speckle pattern data at time intervals sufficient to measure Brownian motion within the interior vessel wall; and comparing the speckle pattern data to a known speckle pattern for a normal blood vessel and a known speckle pattern for an atherosclerotic plaque; wherein speckle pattern data corresponding to a speckle pattern for an atherosclerotic plaque indicates the segment of the blood vessel contains an atherosclerotic plaque. In this method, spatial characteristics of the speckle pattern data can be analyzed to determine structural characteristics of the plaque as described herein.

In another aspect, the invention features a fiber optic probe for detecting speckle patterns in a sample. The probe includes a catheter including a rotatable inner shaft and a transparent outer sheath; a fiber array housed within the shaft and comprising a central optical fiber for transmitting incident light to the sample and multiple optical fibers for transmitting light remitted from the sample; and a mirror arranged near a distal end of the shaft to reflect light passing through the fiber array onto a sample outside the transparent outer sheath and back from the sample through the fiber array. In some embodiments, the shaft can rotate 360 degrees within the sheath, and an inflatable balloon can be connected to the sheath.

The invention further includes an optical system for detecting speckle patterns in a sample. The system has a fiber optic probe as described herein; a coherent light source connected to the central optical fiber within the fiber array; a detector to receive light remitted from the sample; and a processor to process the remitted light and to analyze speckle patterns remitted from the sample. For example, the processor can include a reference speckle pattern or a whole library of reference speckle patterns, e.g., for healthy and diseased tissue. The system can also include an analog-digital converter to convert the analog remitted light into a digital signal.

As used herein, "tissue" means any biological structure in or on a body. Tissue includes aggregates of cells, growths, and deposits such as plaque that may contain lipids or other components. Specific components of plaques that can be investigated include lipid pools, calcifications, fibrous regions, and fibrous caps.

"Speckle" is an interference phenomenon that occurs when coherent light is reflected from a rough or multiply scattering sample onto a detection plane. A "speckle pattern" is the intensity pattern that results from speckle interference.

"Brownian motion" is the random motion of cells, molecules, and other subcomponents within tissue.

"Extrinsic motion" is motion other than Brownian motion. Extrinsic motion includes gross, macroscopic motion of tissue, such motion caused by a heartbeat or other muscle motion, and the movement of fluids in the body, such as blood flow.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a cross-sectional schematic of an optical catheter for gathering speckle data from tissue *in vivo*.

Fig. 2A is a cross-sectional schematic illustrating the catheter of Fig. 1, with an attached angioplasty balloon, inserted within a blood vessel, with the balloon deflated.

Fig. 2B is a cross-sectional schematic illustrating the catheter of Fig. 1, with an attached angioplasty balloon, inserted within a blood vessel, with the balloon inflated.

Fig. 3 is a speckle pattern produced from a cadaveric human aorta using incident light of $\lambda = 632.8$ nm.

Fig. 4 is a schematic illustrating reflectance of incident light from an atherosclerotic plaque.

Fig. 5 is representative raw data speckle images, edge images, and cross-correlation images used to assess the viscosity of a lipid-rich, atherosclerotic plaque in a human aorta.

Fig. 6 is representative raw data speckle images, edge images, and cross-correlation images used to assess the viscosity of normal human aorta tissue.

Fig. 7 is an exponential graph showing speckle decorrelation of an atherosclerotic plaque and aortic tissue over a time interval.

DETAILED DESCRIPTION

At a microscopic level, most tissue is not static. Individual cells move within intercellular fluids, cellular organelles move within cells, and large molecules move back and forth between cells. In non-cellular tissue deposits such as plaques, components such as proteins, lipids, and other molecules also exhibit local motion. These local motions, called "Brownian motion," are essentially random in nature. Measuring and characterizing the Brownian motion of tissues can provide useful information about the structure, composition, and stability of the tissue.

The invention relates to using laser speckle to measure Brownian motion of tissue *in vivo* to gather information about the tissue. In general, coherent light is reflected from a tissue to form a speckle pattern at a detector. Due to motion of reflectors in the tissue, the speckle pattern changes over time, or "decorellates." By monitoring the rate of decorrelation,

while compensating for "extrinsic," or non-Brownian motion of the tissue, Brownian motion in the tissue can be isolated and measured.

In some embodiments of the invention, speckle analysis is used to measure Brownian motion in atherosclerotic plaques to detect plaques that are vulnerable to rupture, and, more specifically, to determine the plaque's vulnerability to rupture. In these embodiments, a modified optical catheter (probe) or other instrument is inserted into a blood vessel (e.g., artery) to locate these plaques, and once a plaque is located, the probe is moved into the proximity of the specific atherosclerotic plaque. Light reflected from the interior wall of the blood vessels, and/or from a plaque, is collected and transmitted to a detector, where a speckle pattern is formed. The speckle patterns of normal tissue and plaque tissue (especially vulnerable plaque tissue) are different, and these differences can be used to detect the plaques. Thereafter, e.g., while compensating for extrinsic motion of the plaque, the speckle pattern is monitored over time to calculate the pattern's rate of decorrelation. From this decorrelation rate, the degree of Brownian motion in the plaque, and therefore the plaque's vulnerability to rupture, can be assessed.

I. Atherosclerotic Plaques

Rupture of an atherosclerotic plaque can lead to acute myocardial infarction, which is a leading cause of death in industrialized countries. When an atherosclerotic plaque ruptures, lipids from the plaque enter the vessel lumen, potentially causing thrombosis, arterial occlusion, myocardial ischemia, and infarction.

According to recent research, plaques vulnerable to rupture generally have a thin, unstable, fibrous cap and a compliant, or "viscous," lipid pool. See, e.g., Virmani et al., "Lesions from sudden coronary death: A comprehensive morphological classification scheme for atherosclerotic lesions," Arterioscler. Thromb. Vasc. Bio., 20:1262-75 (2000) and Lee et al., "The Unstable Atheroma," Arteriosclerosis, Thrombosis & Vascular Biology, 17:1859-67 (1997). The viscous lipid pool applies force to the fibrous cap, compromising the cap and causing rupture. The greater the Brownian motion in the lipid pool, the greater the "viscosity" of the pool, and the more likely the plaque will rupture. Assessing Brownian motion in the lipid pool and measuring the thickness of the fibrous cap *in vivo*, therefore, helps to identify plaques likely to rupture, allowing intervention.

II. Speckle Image Formation

Referring to Fig. 1, a specially modified optical catheter 10 includes a rotatable inner shaft 12 and a transparent outer sheath 14. The inner shaft 12 houses a fiber array 15 and a mirror 16 near its distal end 18. A central fiber 20 in the fiber array connects to a fixed optical fiber 21 that extends from the catheter proximally to a light source 22.

In operation, coherent light, such as laser light, from light source 22 is transmitted via beam-splitter 22a, through the fixed optical fiber 21 and central fiber 20 and onto center 23 of mirror 16. From mirror 16, the light is reflected to a tissue sample 24, such as an atherosclerotic plaque. Outer sheath 14 can be placed directly in contact with sample 24, or can be positioned a short distance, e.g., 1 mm to 10 cm away from the sample. Light enters sample 24, where it is reflected by molecules, cellular debris, proteins, compounds (e.g., cholesterol crystals), and cellular microstructures (such as organelles, microtubules) within the sample. Light remitted from the sample (arrows 26) reflects from mirror 16 to the fibers of array 15, and is then transmitted by array 15 to a planar charge-coupled device (CCD), or a linear or two-dimensional) detector 22b, via a beam-splitter 22a, e.g., located within light source 22. Due to interference, a speckle pattern forms at the CCD detector. The resulting speckle pattern is then digitized by an analog-digital converter, and analyzed using the procedures described in the analysis section below.

The entire shaft 12 can rotate 360 degrees in the direction of arrow R, allowing catheter 10 to gather images around the entire circumference of a sample. For example, catheter 10 can gather images of a plaque around the circumference of a vessel wall.

Since only a few fibers are required to gather adequate speckle data, the diameter of the catheter can be less than 500 μm. Larger diameters are also possible.

Many other types of instruments can be used to gather speckle data. For example, the optics of catheter 10 can be integrated into other types of instruments, such as endoscopes or laparoscopes. The optics can also form a stand-alone unit passed into the accessory port of standard endoscopes or laparoscopes, or integrated into another type of catheter, such as dual-purpose intravascular ultrasound catheter.

The optics can also include a lens that focuses the remitted light 26 onto the distal ends of the fibers in array 15. The lens would allow formation of a "near field image" (near the sample sight) rather than a "far field image" (at the detector).

The catheter can include a polarization filter to remove all but a certain type of polarized light. For example, a cross-polarized filter would allow only light having a polarization perpendicular to the incident light to reach the detector, while a parallel polarized filter would allow only light having the same polarization as the incident light to pass. Since multiply scattered light is less likely to retain its initial polarization than single scattered light, polarization filters can be used to bias the data toward multiply scattered or single scattered light. Such bias can be used to deduce information about the structure of the sample, since light which has penetrated deeper into the sample will be more highly scattered than light reflected from the surface or remitted from near the surface.

Instead of a CCD, the detector can be, e.g., a photographic plate or an array of photodetectors. The light source can illuminate the sample with continuous light or synchronized pulses.

Rather than transmitting the light to the sample through optical fibers, it is also possible to shine light onto a sample in free space. For example, in an open surgical procedure, coherent light in free space could be directed onto a sample with mirrors, and the remitted light then directed to a fiber array. In such free space embodiments, the light source can be, e.g., as far as one meter, or more, away from the sample.

III. Isolation of Brownian Motion

To simplify determining the viscosity of a plaque's lipid pool from changes in a speckle pattern, the temporal changes in the pattern should indicate movement of reflectors within the plaque, but not indicate movement of the plaque itself or movement of reflectors between the detector and the plaque. In other words, the changes in the plaque's speckle pattern preferably reflect Brownian motion, but not extrinsic motion.

To isolate Brownian motion, data is gathered: (1) at time intervals sufficient to detect Brownian motion; and (2) in a manner that compensates for extrinsic motion.

For a time interval to be sufficient to detect Brownian motion, the interval must be long enough to allow for movement of reflectors in the lipid pool, but short enough that the random Brownian movements do not cancel out. For atherosclerotic plaque, an appropriate time interval is about 1-200 ms. Shorter time periods may also be possible. If the time intervals are longer, then changes in the speckle pattern may not adequately differentiate

rapid Brownian movement (indicating high viscosity) from slower Brownian movement (indicating low viscosity).

In the atherosclerotic plaque example, the two most likely sources of extrinsic motion are gross movement of the vessel lumen and plaque tissue due to heartbeats, and blood flow between the plaque and the catheter.

To compensate for gross motion of the plaque due to heartbeats, at least two alternatives are possible. First, the fiber array 15 can be coupled to the plaque tissue using, e.g., an angioplasty balloon. Referring to Fig. 2A, in one embodiment, a balloon 28 is attached to outer sheath 14, on a far side 30 of the catheter. Once the catheter is positioned within a blood vessel in proximity to the plaque, the balloon is inflated. Referring to Fig. 2B, the inflated balloon abuts the vessel wall 32, and presses the catheter against plaque 24, such that a distal region of outer shaft 14 is in direct contact with the plaque. With the catheter coupled to plaque 24 as shown in Fig. 2B, fiber array 15 will move with the plaque when the heart beats, and the gross motion of the plaque will not significantly affect the speckle pattern.

Other methods of coupling the catheter to the plaque are also possible. For example, instead of placing the balloon to the side of the catheter, the balloon can surround the catheter. In this arrangement, a transparent balloon surrounds outer sheath 14, but is also attached to the sheath. When the balloon is inflated, the balloon is squeezed between plaque 24 and wall 32 of the vessel. The balloon, therefore will be in direct contact with the plaque, and will move with the plaque when the heart beats. Since the balloon is attached to shaft 14, and shaft 14 is coupled to array 15, movement of the vessel wall will not significantly affect the speckle pattern. Additional methods of coupling the catheter to tissue can also be used, including methods that do not employ an angioplasty balloon.

A second method of compensating for movement caused by heartbeats is to gather data between heartbeats. In this method, data is gathered during the relatively still PR interval of the diastole of the heartbeat (when the left ventricle is filling with blood). The PR interval lasts for about 0.12-0.2 seconds, providing sufficient time to detect Brownian motion. To insure that data is gathered during diastole, the timing can be computer-controlled or the detector can be linked to an ECG signal, and programmed to gather data only during the PR interval.

To compensate for blood flow between the catheter and the plaque, the catheter can be placed in direct contact with the plaque tissue, as described above, thereby preventing blood from flowing between the detector and the plaque. Alternatively, blood flowing between the plaque and the catheter can be removed and replaced with clear saline solution.

Finally, rather than compensating for extrinsic motion while gathering data, one can compensate for extrinsic motion during the analysis phase by mathematically excluding the extrinsic motion from the analysis, as described below.

IV. Analysis of Speckle Data

Fig. 3 illustrates a typical speckle pattern 40 formed by reflecting light from the wall of a healthy blood vessel. X and Y coordinates overlay pattern 40 to facilitate mathematical description of the pattern. The pattern includes dark patches, where destructive interference dominates, and brighter patches, where constructive interference (or no interference) dominates. Very subtle movements of reflectors within the multiply scattering sample alter the speckle pattern.

By analyzing a series of speckle patterns formed from light reflected from a plaque, one can estimate: (a) the viscosity of a plaque's lipid pool; and (b) the thickness of plaque's fibrous cap. From either or both of these types of data, the plaque's vulnerability to rupture can be assessed.

A. Determining Viscosity of a Plaque's Lipid Pool

There are a number of methods of analyzing speckle data to determine the viscosity of a plaque's lipid pool. By way of example, one method is described in detail in this section and in the Example section below. This method includes: (1) gathering a series of speckle images at short, discreet time intervals; (2) eliminating diffuse reflectance from the data; (3) creating cross-correlation images comparing the speckle images in the series; (4) calculating the maximum correlation between each pair of images to create a one-dimensional data set over time; (5) calculating the rate of decorrelation from the data set; and (6) from the rate of decorrelation, assessing the plaque's viscosity and vulnerability to rupture.

First, using the detection system described above, a series of speckle images are gathered for a plaque at discreet intervals over a period of time. For example, speckle images

can be gathered, e.g., at intervals of every 1, 5, 10, 20, or 30 ms for a time period of, e.g., 200 ms. In general, the shorter the time intervals, the shorter the time period over which data can be gathered. For longer time intervals, such as 30 ms, data can be gathered for, e.g., 1-2 seconds.

Second, to isolate the speckle pattern, the background, non-coherent diffuse reflectance is eliminated from the images. A number of techniques can be used to eliminate the tissue's diffuse reflectance. For example, the raw data speckle images can be converted to edge images. Edge images are spatial derivatives of the raw data images; an edge image reflects the change in intensity of an image as a function of space, at all points in the image, rather than the intensity itself. Known techniques of edge detection include convolution of the image by a kernel (e.g., Sobel or Robert), Morph gradient (subtraction of an eroded, dilated, closed, or opened image by its original), or high pass filtering. Other methods of eliminating background diffuse reflectance include homomorphic filtering, local histogram equalization, or using an optical setup with a small aperture. All of these techniques are well known, and are described, e.g., in Gonzalez, R.C. and Wintz, P., "Digital Image Processing" (Addison-Wesley Publishing Company, Reading MA, 1987) and Jain, Anil, K., "Fundamentals of Digital Image Processing" (Prentice Hall, Englewood Cliffs, NJ, 1987).

After eliminating the non-coherent background reflectance, each speckle image (or edge image) is compared to a reference image in the series (e.g., the t = 0 image) to create a series of cross-correlation images. The cross-correlation images reflect the degree of correlation between the two images as a function of space. From each cross-correlation image, the maximum correlation peak (i.e., the amount of correlation at the point of maximum correlation) is determined using the equation:

$$g(t) = \max\left[\int\int I(x,y,0)I(x+x',y+y',t)dx'dy'\right] \qquad (1)$$

where g(t) is the cross-correlation function, I(x, y) is intensity of the interference at a point (x, y) in the pattern, and t is time. Two-dimensional cross-correlation functions are described generally in Jae S. Lim, "Two-Dimensional Signal Processing" (Prentice Hall, Englewood Cliffs, NJ, 1990) and Jain, Anil, K., "Fundamentals of Digital Image Processing" (Prentice Hall, Englewood Cliffs, NJ, 1987).

By performing the maximum correlation calculations, the cross-correlation images are reduced to a one-dimensional data set as a function of time (i.e., a series of correlation values, each value associated with a time t). From this series of correlation values, a time constant, τ, is calculated, where τ represents the rate of decorrelation. The time constant is the amount of time it takes g(t) to reach (1/e)g(0).

The max function of equation (1) is not the only possible mechanism for reducing the cross-correlation images to a number. For example, image comparisons can be reduced to a representative value by evaluating the cross-correlation function:

$$g(x, y, x_0, y_0, t) = \int\int w(x' - x_0, y' - y_0) I(x, y, 0) I(x + x', y + y', t) dx' dy' \qquad (2)$$

at a point, such as x = y = 0. However, using a point to reduce the image to a value, rather than a max function, would not compensate for the "memory effect" of first order correlation of speckle patterns in turbid media. This "memory effect" is described in Feng et al., Science 251: 633-39 (1991). Advantages to using a point are that a minimum number of fibers and detectors can be used.

From the rate of decorrelation, represented by time constant τ, the viscosity of the plaque's lipid pool can be assessed. In general, the larger τ, the lower the Brownian motion in the lipid pool, and the greater the pool's viscosity. On the other hand, the smaller τ, the greater the Brownian motion in the lipid pool, and the lower the viscosity. The lower the viscosity, the more stresses are exerted on the cap, making the plaque more vulnerable

This information, the viscosity of the plaque's lipid pool, can be used to identify plaques likely or vulnerable to rupture. Specifically, if τ is about 40-100 ms or lower, then the plaque is likely to rupture, and intervention is warranted. If the plaque τ is about 100-200 ms, then the plaque is somewhat vulnerable, but not yet likely to rupture, and should be monitored over time. If the plaque τ is about 200-300 ms, then the plaque is not vulnerable. Non-plaque covered, healthy vessel wall generally has a time constant greater than 300 ms.

B. Determining Thickness of a Plaque's Fibrous Cap

In addition to determining the viscosity of the lipid pool in the plaque, the speckle data can be analyzed to deduce spatial characteristics of the plaque, including the thickness of the fibrous cap. As discussed above, a thin fibrous cap is another indication that a plaque

is vulnerable to rupture. The combination of data relating to viscosity and cap thickness provides the most accurate assessment of plaque vulnerability, although the two characteristics can be assessed and analyzed independently.

Referring to Fig. 4, a typical plaque 50 includes a fibrous cap 52 and a lipid pool 54. Photons that enter plaque 50 (arrow A) are internally scattered by reflectors within the plaque, such as collagen in fibrous cap 52 and lipids in pool 54. The various photons, therefore, exit the plaque at different locations (arrows B). As a result, the speckle pattern (see Fig. 2) has a diameter considerably larger than the width of the original light beam.

The thickness of fibrous cap 52 can be deduced by comparing different regions of the resulting speckle pattern. Referring again to Fig. 3, light forming intensity signals in the outer portion 60 of the pattern traveled greater distances than light forming signals near the center 62 of the pattern. Thus, outer portion 60 of the pattern is formed by photons that, on average, penetrated deeper into the plaque than photons forming center 62. By calculating separate time constants for separate regions of the speckle pattern, the viscosity of the plaque at different depths can be determined. Since the fibrous cap generally exhibits less Brownian motion than the lipid pool, the thickness of the fibrous cap can be estimated from spatially dependent data.

To estimate the thickness of the fibrous cap, separate max cross-correlation functions are described for separate, small regions of the pattern. Each region is defined by a window, w, centered at $(x_o y_o)$:

$$g(x_o, y_o, t) = \max\left[\int\int w(x' - x_o, y' - y_o) I(x, y, 0) I(x + x', y + y', t) dx' dy'\right] \quad (3)$$

Time constants are then calculated from the cross-correlation data for each window, in the manner described above. The variation of τ as a function of the distance from the center of the speckle pattern (i.e., as a function of $(x^2+y^2)^{1/2}$) can then be analyzed to determine the thickness of the fibrous cap. Plaque cap thickness of less than about 60 μm is considered to be vulnerable, but this number can vary to some extent depending on the specific patient. The thickness is estimated by using Monte Carlo simulations to determine decorrelation as a function of $r = \sqrt{x^2 + y^2}$ and fitting experimental data to simulations.

C. Mathematical Compensation for Extrinsic Motion

In addition to providing information about the structural features of a plaque, separately analyzing different regions of a speckle pattern also allows decorrelation caused by extrinsic motion to be identified and removed from the analysis. In general, extrinsic motion caused by gross movement of the plaque tissue or blood flow will be directional and global. By contrast, Brownian motion will be non-directional and non-uniform. Thus, by calculating separate decorrelation functions for different regions of the speckle pattern, decorrelation due to extrinsic motion can be identified and subtracted from the functions, allowing isolation of random, Brownian motion. For example, the position of maximums of cross-correlation functions will shift along a vector $\vec{v}$, which relates extrinsic motion of the sample with respect to the catheter or detection. Brownian motion will decorrelate the speckle patterns in many random directions, and will result in a broadening of the cross-correlation peak and a decrease in correlation maximum above that predicted by linear motion. These two behaviors for intrinsic and extrinsic linear motion should be separable from the cross-correlation function.

V. Additional Imaging Methods

In a simplified system, the rate of decorrelation can be estimated from single pixel speckle images, rather than full, two-dimensional speckle patterns. In this system, a catheter with a single optical fiber could transmit data to a single detector, such as a photodiode. The speckle data gathered would be intensity at the spot as a function of time. From this data, a rate of decorrelation can be calculated directly, without any cross-correlation analysis.

Imaging methods that detect single scattered light, such as optical coherence tomography (OCT) and confocal microscopy, can also be used. While these imaging methods are less sensitive to speckle modulation than the multiple scattering methods described above, they have the advantage of allowing localization of data to a single point within the sample. Such localization would allow measurement of biomechanical properties of the tissue in three dimensions. In addition, in methods that use heterodyne detection, such as OCT, motion of the scatterers can produce a Doppler shift on the returned light. The Doppler shift can provide a further basis for measuring viscosity in the sample. The

mathematics for OCT and confocal microscopy based imaging techniques would be substantially similar to the mathematics described above.

Example

In this example, speckle images formed by reflecting laser light from a cadaveric atherosclerotic plaque in a human aorta were analyzed to assess the plaque's viscosity. A portion of normal aorta was also analyzed for comparison.

At a temperature of 37°C, light from a helium-neon laser (λ = 632.8 nm) was shined on a cadaveric aortic plaque for two seconds. Light reflected from the plaque was received at a CCD camera with a shutter speed of 30 frames per second, through a cross-polarization filter. During the two seconds, the CCD camera recorded a series of 60 speckle images at intervals of 33 ms. Three of the 60 raw data images, corresponding to times t = 0, t = 150 ms, and t = 300 ms, are shown in row A of Fig. 5.

Using IPLab® Spectrum® imaging software, edge detection was performed on the 60 raw speckle images, generating 60 edge images. The three edge images for times t = 0, t = 150 ms, and t = 300 ms are shown in row B of Fig. 5. As discussed above, the edge images reflect the spatial derivative of the raw speckle images (i.e., the light patches in the edge images of row B are locations where the intensity is changing as a function of space).

Using the same software, each of the 60 edge images was then compared to the t = 0 edge image 70 to form 60 cross-correlation images. Each cross-correlation image was generated by multiplying the Fourier transform of the reference image 70 by the complex conjugate of the Fourier transform of the image in question, and then calculating an inverse Fourier transform of the product. For example, referring to row C of Fig. 5, image 72 is an autocorrelation of the t = 0 edge image. Image 72 was formed by multiplying the Fourier transform of reference image 70 by the complex conjugate of the Fourier transform of image 70, and then calculating the inverse Fourier transform of the product. Image 74 was formed by multiplying the Fourier transform of image 70 by the complex conjugate of the Fourier transform of the t = 150 ms edge image, and then calculating the inverse Fourier transform of the product.

Each cross-correlation image represents the degree of correlation between the corresponding edge image and the reference edge image 70 (i.e., brighter spots are locations where there is a higher degree of correlation than at darker spots).

From each cross-correlation image, the maximum cross-correlation peak (i.e., the correlation at the maximum point of correlation) was calculated using equation (1). The resulting data set included 60 cross-correlation values, each value associated with a time t.

A set of images of normal aorta tissue is shown in Fig. 6. These images are comparable to the set of images in Fig. 5 for a lipid-rich plaque in the same aorta and were imaged and processed in the same manner.

The maximum cross-correlation data for the lipid-rich plaque and the normal aorta tissue were then fit to an exponential cross-correlation function, $G(\tau)$, using Igor Pro®, v 3.01 software (Wavemetrics, Inc). The resulting exponential function was graphed in Fig. 7, curve 80. By way of comparison, the exponential cross-correlation function for speckle data taken from healthy cadaveric aortic tissue is shown in curve 82. The data for curve 82 was gathered and processed using the same procedures as the data for curve 80.

From the cross-correlation data, the decorrelation rate, represented by the time constant τ, was calculated. For the plaque, the time constant was 40 ms. For the aortic tissue, the time constant was 500 ms.

Based on these data, the plaque was borderline vulnerable. Thus, had this plaque been analyzed *in vivo*, using the procedures described above, a physician would have determined that the plaque was a possible candidate for rupture, and may have chosen to intervene, preventing a possible infarction.

OTHER EMBODIMENTS

The methods described herein can also be used to characterize diseased tissue other than atherosclerotic plaques. The microscopic and macroscopic constituents of diseased tissue differ as compared to normal non-pathologic counterparts. For example, speckle patterns can be used to diagnose and characterize other tissue pathology such as neoplasia (cancer), infection, tissue viability, or healing response to injury. In the case of neoplasia, tumors typically have an abnormal abundance of one cell type (clonal) and a surrounding abnormal supporting matrix. This cell type may produce and secrete a viscous fluid, such as

mucin in adenocarcinoma, which would result in lower speckle decorrelation time constants than normal non-cancerous tissue. Moreover, the surrounding matrix may be composed of necrotic tissue and an abundance of abnormal vessels that would also serve to decrease the speckle decorrelation time constant. Other tumors, like osteosarcoma, produce osteoid or immature bone that would increase the time constant compared to normal tissue. Other forms of neoplasia would have increased time constants due to desmoplastic (abundant) fibrous stroma initiated by cytokines produced by the tumor. Indeed, many tumors, including bronchogenic carcinomas and breast carcinomas are firm upon gross examination due to the fibrous stroma surrounding the malignant cells. This fibrous stroma would increase the time constant relative to surrounding normal tissue.

In other examples, in the case of infection, abscesses will be more viscous than surrounding tissue, enabling identification of the infected region by measuring a decrease in the time constant. Inflammation, manifested by the influx of activated inflammatory cells will be characterized by a decrease in the speckle decorrelation time constant as these cells degrade the normal supporting tissue in response to a the presence of bacterial, viral, or foreign body antigens. Necrotic tissue, such as burn eschar, diabetic ulcers, necrotic bowel, and ischemic myocardium will have longer time constants than viable tissue from the same organ due to the lack of intravascular and extravascular fluid and flow in these extracellular spaces.

In the case of healing, fibrosis and fibrous remodeling will likely have longer time constants due to the abundance of collagen matrix and granulation tissue, which would not be present in uninjured tissue. Speckle decorrelation times may also be used to estimate tissue hydration and provide a means for quantifying the state of hydration in a patient. While the above examples elucidate some of the mechanisms that explain how disease affects the biomechanical properties of pathologic tissue, many more exist and are well known in the field of gross anatomic pathology. These differing biomechanical properties can be measured by speckle for the purpose of screening, intraoperative margin identification, and primary diagnosis.

The foregoing detailed description is intended to illustrate and not limit the scope of the invention, which is defined by the appended claims. Other aspects, advantages, and modifications are within the scope of the claims.

What is claimed is:

1. A method of analyzing tissue, the method comprising:

illuminating a tissue with coherent light;

receiving light reflected from the tissue at a detector to form a series of speckle patterns; and

analyzing changes in the speckle patterns at time intervals sufficient to measure changes caused by Brownian motion of objects within the tissue.

2. The method of claim 1, further comprising compensating for extrinsic motion to isolate the Brownian motion.

3. The method of claim 1, wherein the tissue is *in vivo*.

4. The method of claim 1, wherein the tissue is internal tissue.

5. The method of claim 4, wherein the illuminating step comprises providing an invasive device coupled to a light source, passing the device into a patient, placing the device in proximity to the tissue, and shining coherent light from the light source onto the tissue.

6. The method of claim 5, wherein the invasive device is selected from the group consisting of a catheter, an endoscope, and a laparoscope.

7. The method of claim 5, wherein the placing step includes placing the device in direct contact with the tissue.

8. The method of claim 5, wherein the invasive device comprises a catheter having a first fiber that transmits light from the light source to the tissue, and a fiber array that receives light remitted from the tissue.

9. The method of claim 1, wherein the coherent light comprises laser light.

10. The method of claim 1, wherein the speckle pattern is a far field image formed at the detector.

11. The method of claim 1, wherein the analyzing step comprises comparing each of the series of speckle patterns to a reference speckle pattern, and quantifying the differences between each pattern and the reference pattern.

12. The method of claim 11, wherein the analyzing step comprises digitizing each of the speckle patterns, and the quantifying step comprises evaluating a maximum cross-correlation between each pattern and the reference pattern.

13. The method of claim 12, wherein the analyzing step further comprises determining a decorrelation rate for the speckle patterns.

14. The method of claim 1, wherein the analyzing step further comprises analyzing spatial characteristics of the speckle pattern to deduce structural characteristics of the tissue.

15. The method of claim 14, wherein the illuminating step comprises illuminating multiple sections of the tissue in succession, the receiving step comprises forming a separate series of speckle patterns for each respective section of the tissue, and the analyzing step comprises analyzing each separate series of speckle patterns and comparing the separate series to deduce structural differences between the respective sections of the tissue.

16. The method of claim 2, wherein compensating for extrinsic motion comprises performing the receiving step during a diastole of a heartbeat.

17. The method of claim 2, wherein the receiving step comprises gathering reflected light at a light receptor and transmitting the gathered light to the detector, and wherein compensating for extrinsic motion includes coupling the receptor to the tissue.

18. The method of claim 2, wherein compensating for extrinsic motion includes excluding changes in the speckle patterns caused by non-random motion during the analysis step.

19. The method of claim 2, wherein extrinsic motion results from blood flow between the tissue and the reflector, and the compensating step comprises replacing the blood with a transparent solution.

20. The method of claim 1, wherein the tissue comprises atherosclerotic plaque.

21. A method of determining the susceptibility to rupture of an atherosclerotic plaque having a lipid pool and a fibrous cap, the method comprising:

illuminating the plaque with coherent light;

receiving light reflected from the plaque at a detector to form a series of speckle patterns;

gathering speckle pattern data at time intervals sufficient to measure Brownian motion within the lipid pool; and

assessing the plaque's vulnerability to rupture from the amount of Brownian motion.

22. The method of claim 21, further comprising analyzing spatial characteristics of the speckle pattern data to determine structural characteristics of the plaque.

23. The method of claim 22, wherein the analyzing step comprises assessing the thickness of the fibrous cap.

24. The method of claim 23, wherein a plaque is considered vulnerable to rupture if the thickness of the fibrous cap is less than about 60 microns.

25. The method of claim 22, wherein the analyzing step comprises assessing the viscosity of the lipid pool.

26. The method of claim 25, wherein the plaque is considered vulnerable to rupture if the viscosity of the lipid pool has a time constant of less than about 200 milliseconds.

27. The method of claim 25, wherein the plaque is considered likely to rupture if the viscosity of the lipid pool has a time constant of less than about 100 milliseconds.

28. A method of detecting a vulnerable atherosclerotic plaque having a lipid pool and a fibrous cap within a blood vessel, the method comprising:

illuminating a segment of the blood vessel *in vivo* with coherent light;

receiving light reflected from the interior vessel wall of the segment at a detector to form a series of speckle patterns;

gathering speckle pattern data at time intervals sufficient to measure Brownian motion within the interior vessel wall; and

comparing the speckle pattern data to a known speckle pattern for a normal blood vessel and a known speckle pattern for an atherosclerotic plaque;

wherein speckle pattern data corresponding to a speckle pattern for an atherosclerotic plaque indicates the segment of the blood vessel contains an atherosclerotic plaque.

29. The method of claim 28, further comprising analyzing spatial characteristics of the speckle pattern data to determine structural characteristics of the plaque.

30. The method of claim 29, wherein the analyzing step comprises assessing the thickness of the fibrous cap.

31. The method of claim 30, wherein a plaque is considered vulnerable to rupture if the thickness of the fibrous cap is less than about 60 microns.

32. The method of claim 29, wherein the analyzing step comprises assessing the viscosity of the lipid pool.

33. The method of claim 32, wherein the plaque is considered vulnerable to rupture if the viscosity of the lipid pool has a time constant of less than about 200 milliseconds.

34. The method of claim 32, wherein the plaque is considered likely to rupture if the viscosity of the lipid pool has a time constant of less than about 100 milliseconds.

35. A fiber optic probe for detecting speckle patterns in a sample, the probe comprising

a catheter including a rotatable inner shaft and a transparent outer sheath;

a fiber array housed within the shaft and comprising a central optical fiber for transmitting incident light to the sample and multiple optical fibers for transmitting light remitted from the sample; and

a mirror arranged near a distal end of the shaft to reflect light passing through the fiber array onto a sample outside the transparent outer sheath and back from the sample through the fiber array.

36. The fiber optic probe of claim 35, wherein the shaft can rotate 360 degrees within the sheath.

37. The fiber optic probe of claim 35, further comprising an inflatable balloon connected to the sheath.

38. An optical system for detecting speckle patterns in a sample, the system comprising

a fiber optic probe of claim 35;

a coherent light source connected to the central optical fiber within the fiber array;

a detector to receive light remitted from the sample; and

a processor to process the remitted light and to analyze speckle patterns remitted from the sample.

39. The system of claim 38, wherein the processor comprises a reference speckle pattern.

40. The system of claim 38, wherein the processor comprises an analog-digital converter to convert the analog remitted light into a digital signal.

ABSTRACT

The invention relates to methods and systems to optically analyze samples such as tissue based on speckle patterns of Brownian motion.

Fig. 1

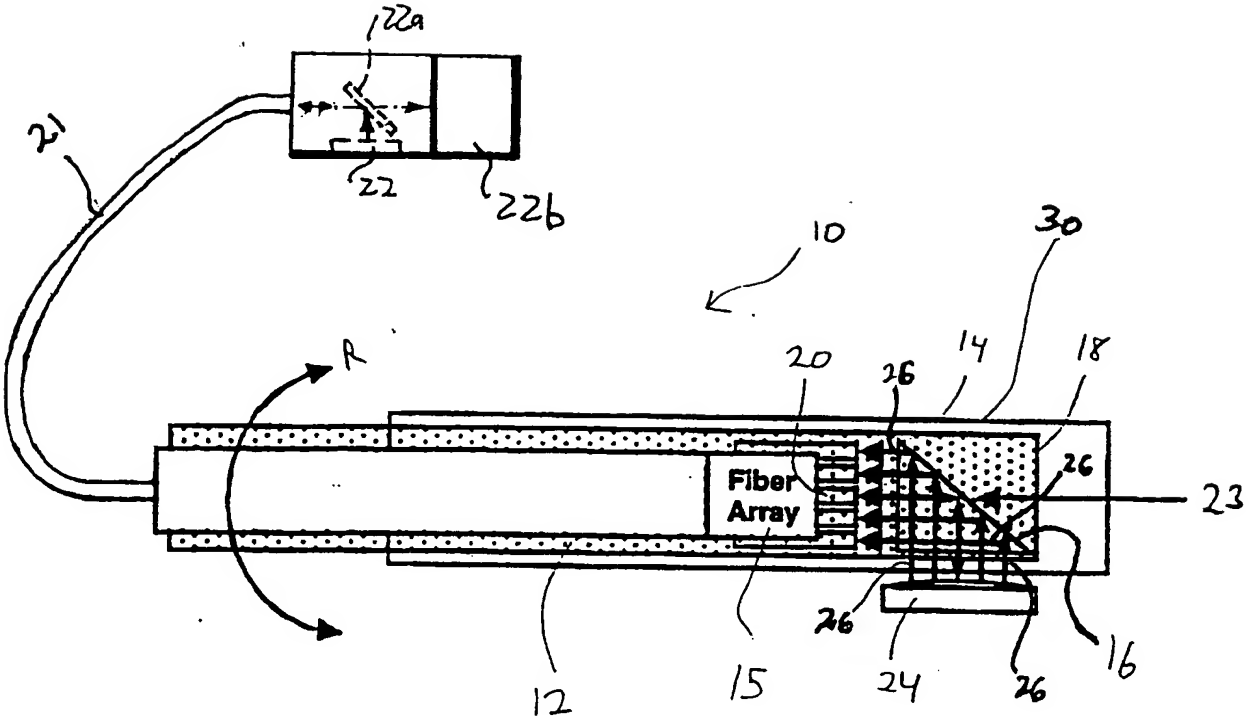


Fig. 2A

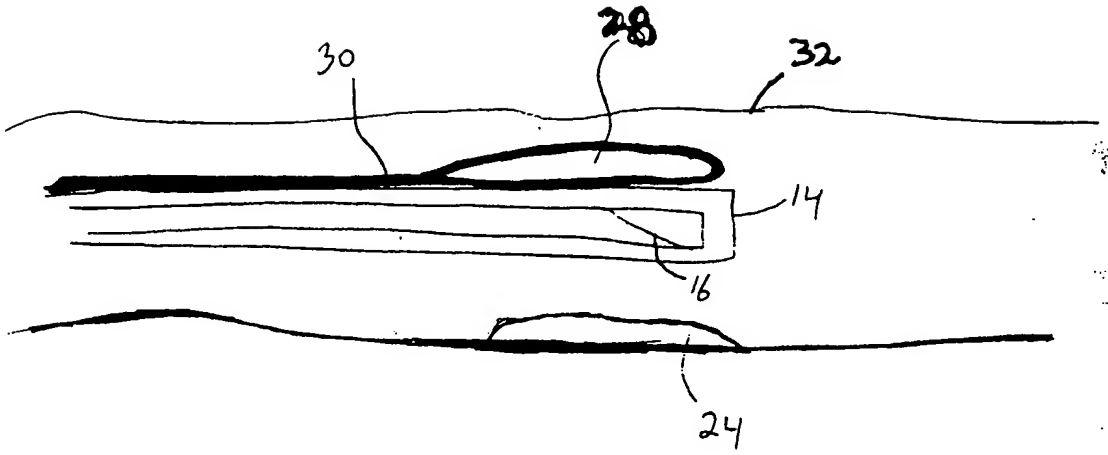


Fig. 2B

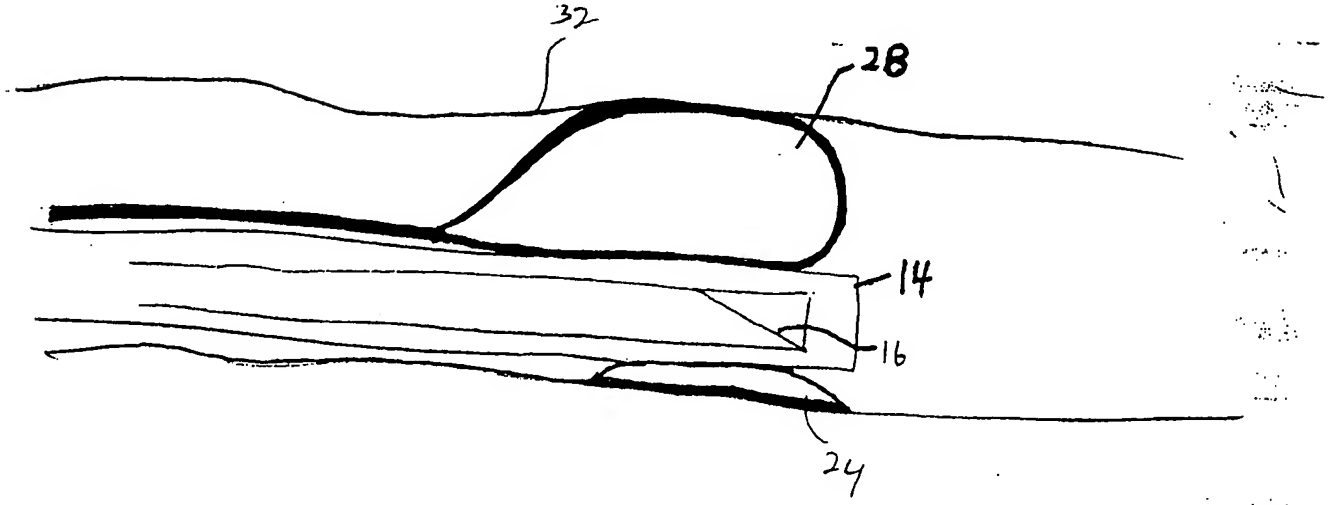


Figure 3

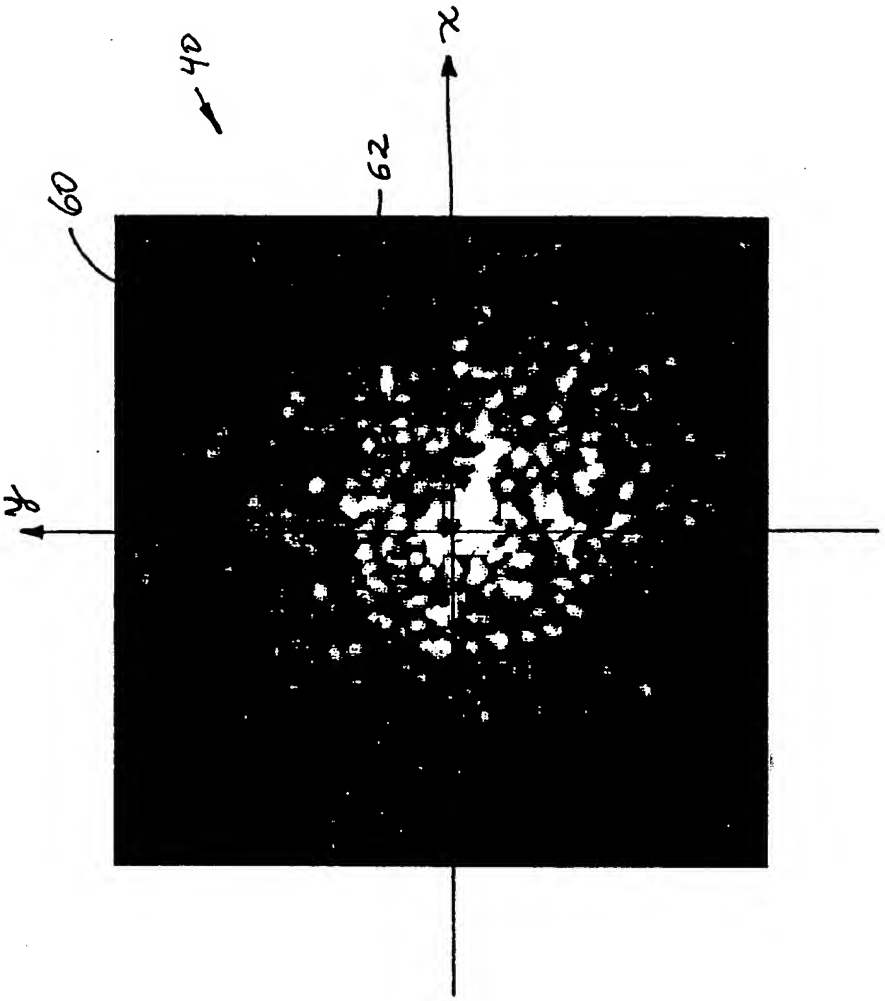
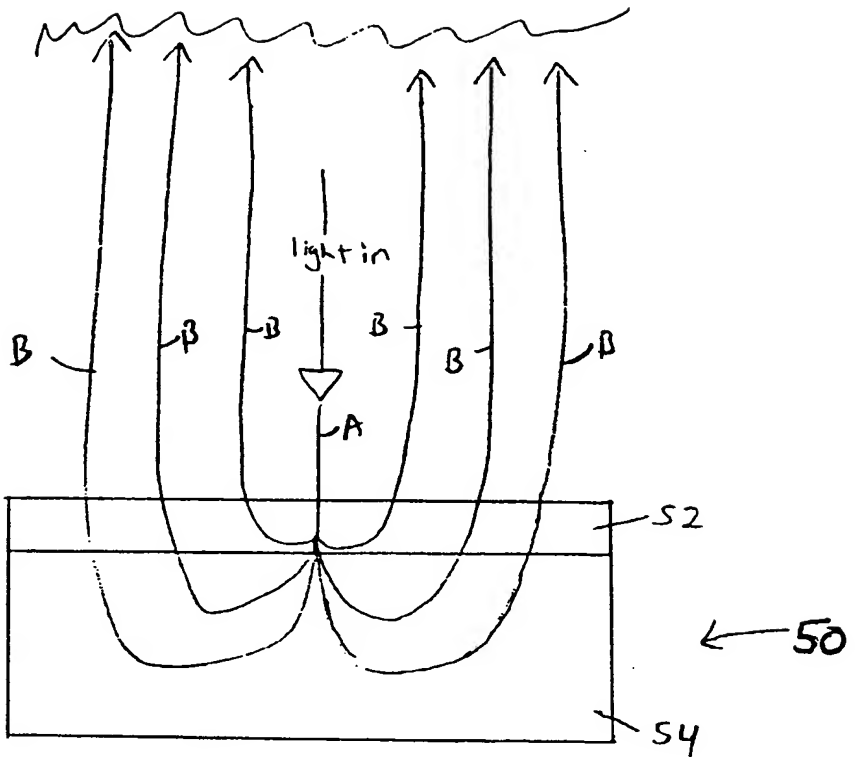


Fig. 4



Lipid-rich plaque

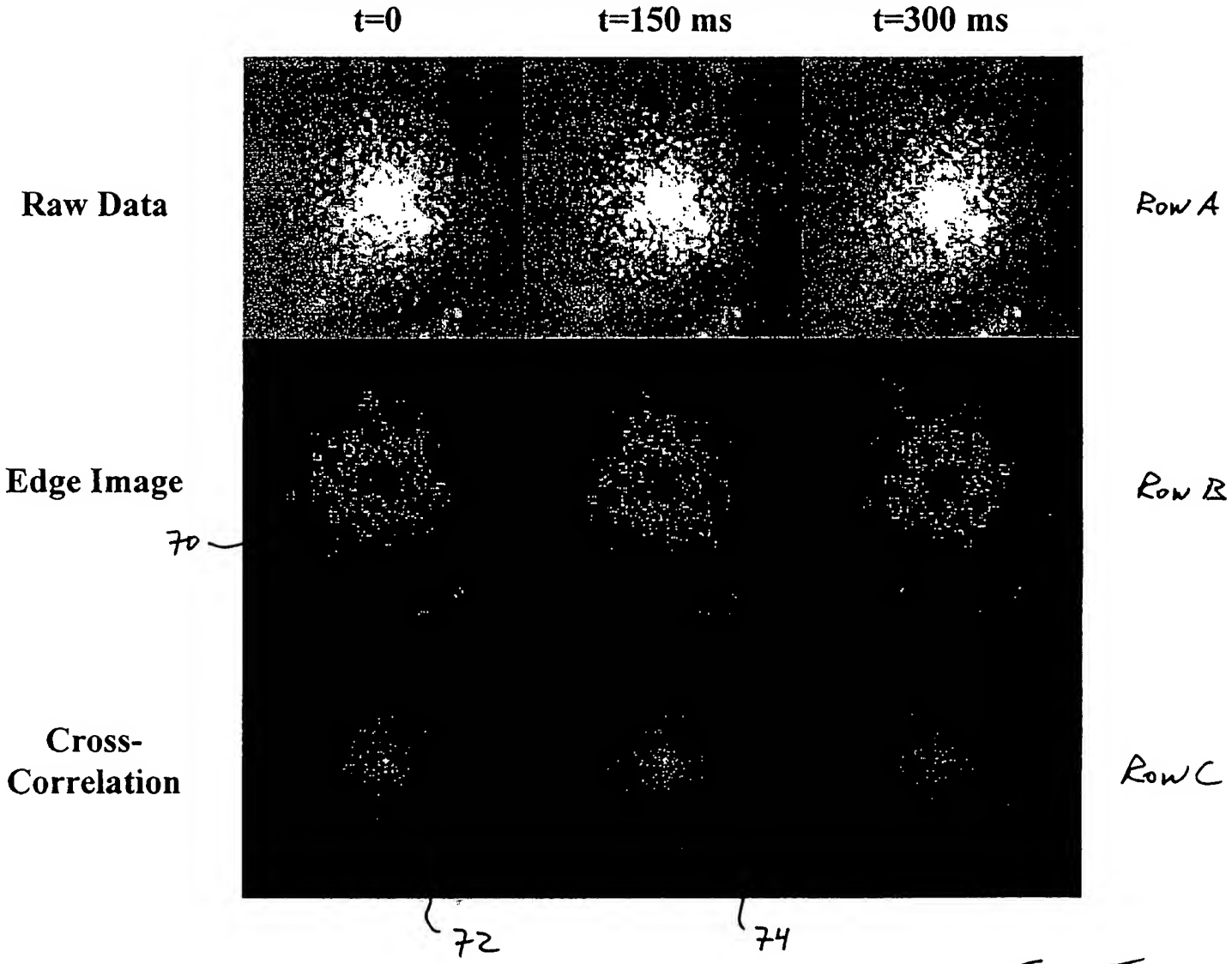


Fig. 5

Normal Aorta

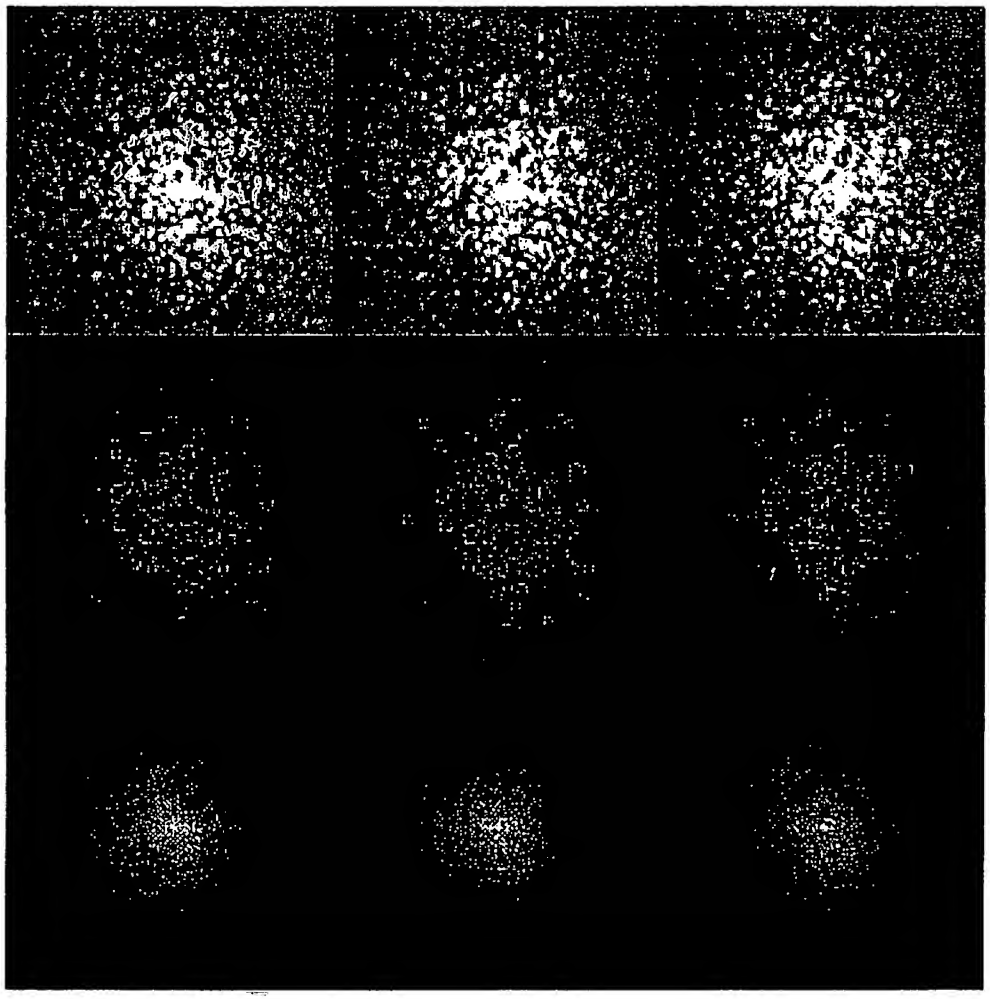


Fig. 6

Lipid-rich Aortic Plaque vs. Normal Aorta
Speckle Correlation
(Perpendicular Polarization)
(Exponenial Fits of Raw Data)

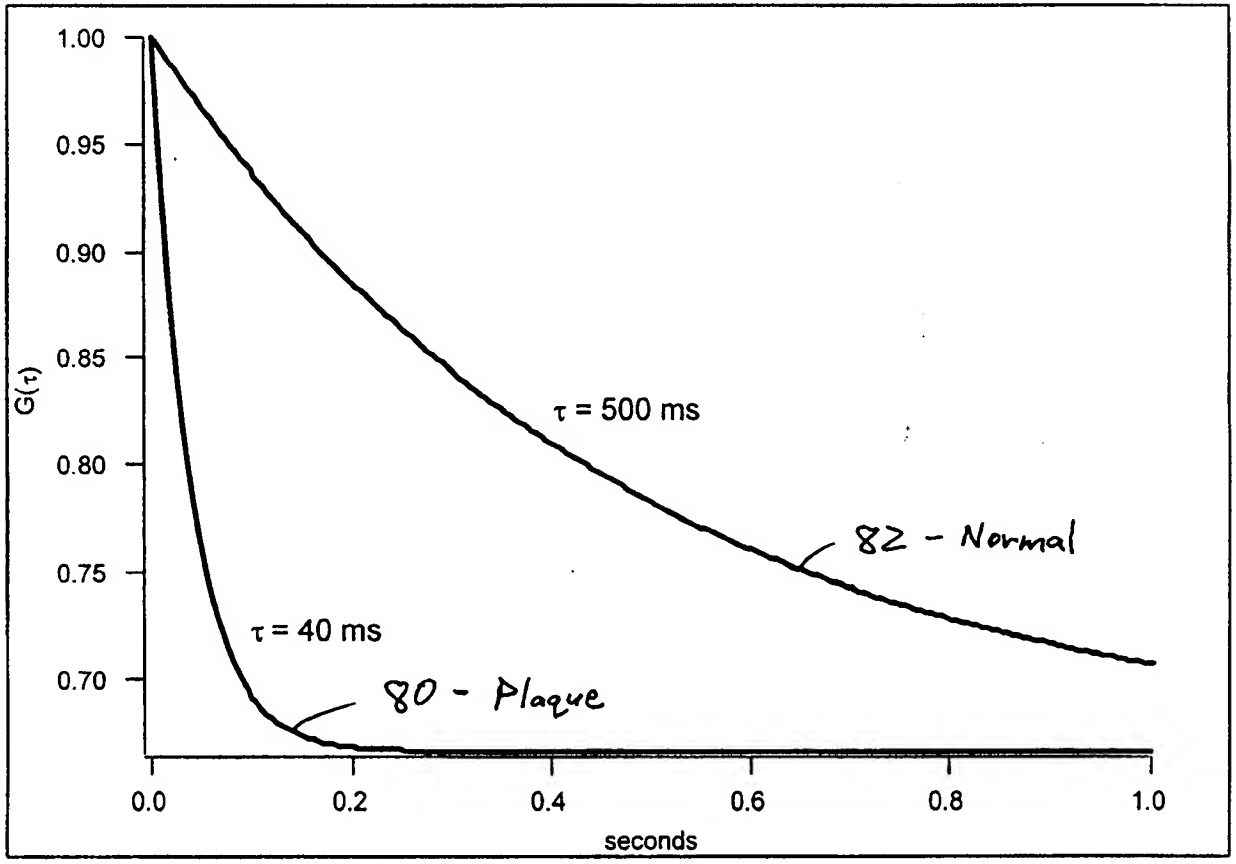


Fig. 7